Buprenorphine Treatment for Opioid Addiction in the Primary Care Setting: Predictors of Treatment Success and Failure

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Glossary of Abbreviations

AA: Alcoholics Anonymous

BUP: Buprenorphine

NA: Narcotics Anonymous

EMR: Electronic Medical Record

MGH: Massachusetts General Hospital

MGH CHCC: Massachusetts General Hospital Charlestown HealthCare Center

MJ: Marijuana

MMT: Methadone Maintenance Therapy

MRN: Medical Record Number

OD: Overdose

QPID: Queriable Patient Inference Dossier

RPDR: Research Patient Data Registry

I. Introduction

Recent estimates suggest that two million people in the United States are currently dependent on opioid drugs.[1] In 2010, the Global Burden of Disease Study reported that approximately 15.5 million opioid dependent individuals exist globally, and that the estimated morbidity caused by opioid dependence had increased by nearly 75% from the prior study in 1990.[2] Opioid overdose is now the second most common cause of accidental death in the United States, and opioid addiction is the cause of well-documented increases in the risks of depression, suicide, HIV and Hepatitis C.[3] With respect to the financial burden of disease, in 2001 the total cost of prescription opioid misuse alone was greater than 8 billion dollars; earlier studies have estimated that annual direct health care costs for opioid users average nearly 9x higher than non-opioid users.[4] Despite this, fewer than 10% of people who struggle with addiction receive appropriate pharmacologic therapy.[5]

Buprenorphine is a partial mu-opioid receptor agonist that was approved by the FDA in 2002 for use in treating opioid addiction.[6] The number of prescriptions for buprenorphine formulations has nearly doubled every year since, with an estimated 6 million prescriptions written in 2009.[7] This trend has been bolstered by numerous randomized controlled trials showing that buprenorphine can perform as well as methadone in reducing illicit opioid use among patients with opioid addiction.[8] Documented advantages of buprenorphine treatment over methadone include lower risk of toxicity/overdose, access at office-based practices, lower abuse potential, milder withdrawal symptoms, and ability to self-administer medications at home.[9]

Understanding the potential for medical therapies in this realm is a pressing need. In response to the widespread problem of drug addiction, the Affordable Care Act named 'Substance Use Disorders' one of the 10 elements of its Essential Health Benefits, requiring all health insurance policies purchased on insurance exchanges to fully cover treatment and support for substance use disorders.[10] Parallel increases in the rates of opioid addiction, physician comfort with using buprenorphine, and access to addiction treatment can be expected to increase the demand for quality, evidence-based addiction therapy. Despite the growing use of buprenorphine and the burden of opioid addiction, only a small number of studies have investigated which factors influence success or failure of opioid replacement therapy, especially when treatment is initiated in the primary care setting.

This project aims to build upon prior work and pave the way for objective tools that physicians can use to analyze a given patient's prognosis for addiction treatment with buprenorphine. By investigating easily observable, definable patient characteristics and creating models that predict patient outcome, we hope not only to uncover the psychosocial determinants of treatment response, but to identify ways in which physicians can risk-stratify patients who are interested in buprenorphine therapy, and allocate their support resources accordingly.

A number of prior studies have pursued answers to similar, related questions, which helped to shed light on the variables we chose to investigate. For example, a 2007 study which investigated an overlapping population followed a cohort of 99 patients who were on a buprenorphine care protocol at one of two primary care clinics, and looked for predictive correlates of physician-judged sobriety at the end of 6 months, finding that private insurance, older age, and attendance at self-help meetings correlated with treatment success.[11] By documenting a 'success rate' of 54%, they concluded that outpatient buprenorphine treatment in a primary care setting is a viable model for addiction care delivery. Another study, focusing exclusively on prescription opioid use also found increased age to correlate with success at 12 weeks, but also found relationships between success and a diagnosis of depression, first time treatment, and negative history of injection drug use.[12] Studies using even shorter follow up periods of 4 weeks found age, lack of criminal history, and decreased frequency/dose of opioid use to be correlated with sobriety.[13] Finally, one of the largest analyses of this type examined 382 patients with a one year follow up period; again, older patients fared better, in addition to patients who were employed, and interestingly, those who had used buprenorphine which they had purchased on the street.[14]

Building upon this foundation, we performed a retrospective cohort analysis on 10 years of data from 160 patients who received buprenorphine therapy for opioid addiction at a community health center in Boston. Data were collected via intensive chart review on 36 demographic, psychosocial, and medical variables. Patients were followed for 1 year after initiating buprenorphine therapy, and were assigned to outcome groups based on objective toxicology screens. Finally, two levels of statistical analysis were performed to uncover both unadjusted, and adjusted logistic predictors of treatment success and failure.

This study offers several qualities that distinguish it from the majority of prior work on the topic. First, it has the benefit of a longer, longitudinal follow-up period than most pre-existing studies. While no consensus exists as to what constitutes absolute 'treatment success,' a number of comparable studies have used single drug tests at 4 or 12 weeks as a proxy for sobriety.[12,13] Our approach can be expected to better capture the nature of addiction as a chronic disease, and account for the commonly occurring relapses or losses to follow-up that may occur well into the course of treatment. Next, to our knowledge, no prior studies have used a three-pronged approach to defining patient outcome (described in detail below). We believe that outcome categories of 'Early Failure,' 'Late Failure,' and 'Long-term Success' better reflect clinical realities, and exceed the ability of traditional dichotomous success/failure groupings to capture the true heterogeneity that exists in treatment responses. Finally, recent studies have uncovered the changing demographics of patients who are suffering from opioid addiction. What was once an inner-city issue affecting mostly minorities now predominantly affects young whites who live in peri-urban regions.[15] Our study population perfectly mirrors the 'new face' of opioid addiction, and is therefore of increased relevance to the problems that physicians will face in the coming years.

With an increasing amount of addiction occurring in such peri-urban areas, the demand for outpatient primary care based addiction treatment will increase. For this reason, deriving the best ways to provide addiction care is increasingly relevant. To this end, this study attempts to answer the following questions:

1) Which patients with opioid addiction can be expected to achieve long-term success with buprenorphine therapy?
2) Which patients are expected to fail treatment at the outset, during the induction phase?
3) Which patients have a high risk of relapse during the course of treatment?

We hope that the answers to these questions can not only inform which patients would benefit from extra resources, but also generate implementable ideas about how best to support patients through their recovery from opioid addiction.

II. Methods

Subject Selection

All patients considered for inclusion in this study were seen over the past 10 years at the MGH Charlestown HealthCare Center (MGH CHCC) for long-term buprenorphine maintenance therapy for opioid addiction. Individual subjects were all selected using the Partners Research Patient Data Registry (RPDR) data query tool.[16] RPDR is a centralized clinical data source, which accesses and compiles patient data via a number of online platforms. The program was asked to pull the names of patients who met two overlapping basic criteria: 1) Patients who have been seen for medical care at Charlestown HealthCare Center, and 2) Patients who have received a prescription for a buprenorphine formulation. The program retrieved a total of 380 patients who were members of both groups, and a total of 300 patients were investigated at random from this cohort. After 140 were excluded, 160 subjects were included in the final study. Please see Table 1 for Exclusion Criteria.

Table 1: EXCLUSION CRITERIA

- Patient received buprenorphine therapy from a provider *outside* MGH Charlestown
- Patient initiated buprenorphine therapy >10 years ago
- Patient initiated buprenorphine therapy <1 year ago (thus had insufficient time for follow-up)
- Patient was prescribed buprenorphine for pain, *without* signs/symptoms of opioid addiction
- Patient was already stable on buprenorphine and was accepted as a care transfer
- Patient was prescribed buprenorphine merely as a temporary bridge to other therapy
- Patient's medical record had insufficient documentation to determine above criteria

Treatment Protocols

This retrospective study did not enforce treatment protocols; instead, all clinical decisions were dictated by each individual buprenorphine provider. Patients thus varied in their prescribed buprenorphine regimen, frequency of visits, participation in counseling, induction protocol, and threshold for continuation/discontinuation of therapy. Frequency of follow-up visits also differed based on patient response to therapy, availability, and

patient comfort, such that some patients were seen weekly, and others monthly or bimonthly.

However, since the study was performed using only patients who were seen at one site, significant continuity exists concerning the general framework of intake and care. All participating physicians were certified in the appropriate provision of buprenorphine to patients with opioid addiction. All patients were either self-referred, or referred by other practitioners in the area, and participated in treatment voluntarily. No outreach was undertaken. Since the buprenorphine practice at MGH CHCC is often saturated, many patients were placed on a wait-list until spots became available for them to participate in treatment. All patients were seen initially by a physician for evaluation of candidacy in the buprenorphine program, and in almost all circumstances, this visit was supplemented by an additional intake visit with a social worker or psychologist, in which comprehensive drug use and social histories were obtained.

If patients were deemed to be suitable candidates for therapy based on a stated commitment to attend appointments and maintain open communication with doctors, they presented to the clinic for buprenorphine induction. At that appointment, a drug screen was performed, and the patient received a prescription for a limited quantity of buprenorphine at a dose ranging from 4-16mg/day. Patients were instructed to return for a prescription refill and a repeat toxicology screen at the end of an allotted interval. At that appointment, results of any prior toxicology screens would be discussed, and plans for the best way to proceed with treatment would be discussed. All patients were seen on a regular basis and received toxicology screens for the duration of their care. All patients were also strongly encouraged to participate in dedicated drug counseling sessions; both one-on-one and group therapy options were available.

Data Collection

Patients were identified using their 7-digit MGH medical record number (MRN), which was produced as part of the RPDR data query. All detailed health information was obtained using the Queriable Patient Inference Dossier (QPID). QPID is an online platform, which intelligently searches a patient's electronic medical records and returns tailored, relevant results. It is unique in that it is able to search by 'concept' or 'topic' and retrieve

broader results than simple verbatim matches between the query term and patient data. QPID draws upon all available electronic health information, from patient notes entered by physicians to laboratory results and up to date comprehensive demographic data. For each patient in the study, a specific QPID search algorithm was used to retrieve all data (see Table 2 for details).

All data were collected solely by the author of this manuscript. The data were collected in two stages. First, all necessary information was obtained concerning patient demographics and predictive variables. At this time, the query was blind to information concerning patient outcome, in order to minimize bias. Once this phase was completed for all subjects, another phase was initiated in which data were collected purely on outcome variables, this time blinded to predictor variables for the same reason. Final data values for each variable were determined by a comprehensive integration of all available information from clinical and laboratory data, including systematic intake notes completed on most patients.

All data were entered into REDcap, a secure web application for building and managing online data sets.[17] In this way, data were stored online in a non-centralized, non-traceable fashion. Before data collection began, the author of this manuscript designed a custom data collection tool with built-in mechanisms to protect data accuracy and prevent errors. For example, possible ranges of numerical data were restricted, dates were specifically coded, missing/equivocal fields were made to trigger flags, and drop-down menus were designed to accommodate categorical variables. Once data collection was complete, REDCap was used to compile and export all of the coded data into an Excel file, which was used for statistical analysis.

Table 2: VARIABLES: DEFINITIONS AND SEARCH STRATEGY

Predictive Variable	Definition	QPID Search Strategy
Age	At time of induction	'Demographics'
Sex	Male or Female	'Demographics'
Induction Date	Date of 1st prescription for buprenorphine	'suboxone,' 'buprenorphine,' 'bup,' 'induction'
Injection Drug Use	Any history of injection opioid use	'heroin,' 'IV,' 'intravenous,' 'injection,' 'IVDU'
Intranasal Drug Use	History of sniffing, snorting crushed opioids. Cocaine not included	'intranasal,' 'snort,' 'nasal,' 'sniff'
Years of Active Use	Years since first opioid use, subtracting all periods of abstinence	When exact value not recorded, estimates were made using all available information
Cocaine use	Endorsed use within 1 week of induction	'cocaine,' 'coke,' 'crack'
Alcohol use	Endorsed use within 1 week of induction, includes binge episodes or >2 drinks/day	'drinks,' 'drinker,' 'alcohol'
Cigarette use	Active smoking	'smoker,' 'smokes,' 'cigarettes,' 'pack(s)'
Marijuana use	Endorsed use within 1 week of induction	'marijuana,' 'mj,' 'weed,'
Non-prescription Benzodiazepine use	Endorsed use within 1 week of induction	'benzo,' 'benzos,' 'xanax'
Non-prescription Buprenorphine use	Endorsed use of non-prescription buprenorphine at any point in the past	'street,' 'suboxone,' 'buprenorphine'
Prior Buprenorphine attempt	Prior official, physician supported attempt at buprenorphine maintenance	'buprenorphine,' 'bup,' 'suboxone'
Prior Methadone attempt	Prior official, physician supported attempt at methadone maintenance	'methadone,' 'mmt'
Prior Detox attempt	Prior official attempt at inpatient or intensive outpatient detoxification	'detox'
History of Overdose	Verbal endorsement or EMR evidence of least 1 prior drug overdose	'od,' 'overdose'
Employment status	Patient endorses being employed in any capacity at the time of induction	'work,' 'employment,' 'unemployed,' 'job'
Prescribed SSRI, Benzodiazepine, Gaba analogue, Antipsychotic, Mood Stabilizer	At induction or any time during first month of treatment	'medications'
Buprenorphine Dose	Initial per/day dose	'medications'
Depression	Axis I diagnosis of depression or presence of 'depression' on problem list	'depression,' 'depressed'
Anxiety Disorder	Axis I diagnosis of anxiety or presence of 'anxiety' on problem list	'anxiety,' 'panic,' 'panic attacks,' 'generalized anxiety disorder'
Bipolar Disorder	Axis I diagnosis of bipolar or presence of	'bipolar,' 'mania,' 'manic'

	'bipolar' on problem list	
Psychosis	Axis I diagnosis of psychosis or presence of 'psychosis' on problem list	'psychosis,' 'psychotic,' 'schizophrenia'
PTSD	Axis I diagnosis of PTSD or presence of 'PTSD' on problem list	'PTSD,' 'trauma'
Chronic Pain	History of chronic pain, or persistent presence of 'chronic pain' on problem list	'chronic pain,' 'pain'
Race	White, Black, Latino, Asian, other	'race'
History of Incarceration	Any history of time in jail prior to induction	'jail,' 'prison,' 'incarceration,' 'incarcerated'
History of Homelessness	Any history of time spent living on the street, or otherwise without a home	'homeless,' 'street'
Participation in Drug Counseling	Participation in >3 sessions with an MGH CHCC psychotherapist or social worker	Scrolled by date to find visit notes, or 'no show' notes
Participation in AA/NA	Endorsed attendance at numerous AA/NA meetings within first month of treatment.	'aa,' 'meetings,' 'na'
HIV Seropositivity	History of positive HIV Elisa or PCR	'HIV,' 'AIDS'
Hepatitis C Seropositivity	History of positive Hepatitis C antibody	'hepatitis,' 'hepatitis c,' 'hep c'

Outcome measures

All outcome measures were determined by the results of toxicology screens. Various toxicology screening methods were used over the past 10 years at the MGH CHCC, including urine, serum and saliva based tests. Data were collected for 1 year after the day patients began taking buprenorphine, unless treatment was discontinued or the patient was lost to follow-up. The outcome observation period was broken up into two parts: the first 8 weeks, or 'early treatment' period, and the following 10 months, or the 'late treatment' period. During the first 8 weeks, data were collected about the absolute number of toxicology screens that a patient received, and also the number of those screens that were positive for opioids. 'Positive' toxicology screens were defined as any that showed evidence of primary, non-buprenorphine opioids in body fluids, including but not limited to heroin, oxycontin, oxycodone, hydrocodone, codeine, and methadone. Because opioid metabolites were not included in all toxicology screens, they were not used in this study as evidence of drug use. The number of toxicology screens which were positive for cocaine was also measured as a secondary outcome. The presence of other drugs, such as marijuana, benzodiazepines, and amphetamines were not included in the study. The toxicology screen administered on the

day of buprenorphine induction was also excluded—nearly all screens are positive, and the information was thus of limited value.

Based on their toxicology screens, all patients were subdivided into one of three primary outcome groups. Patients who were lost to follow-up, or whose treatment was discontinued less than 2 months after induction were considered 'early failures.' If patients attended appointments and were retained in care for at least 8 weeks, they were not considered early failures regardless of their toxicology screen results. This decision was made to account for those patients who exhibited a 'slow' or 'bumpy' start on buprenorphine therapy but later achieved sobriety. Patients who were retained in care for more than 2 months, but who then demonstrated ≥ 4 positive toxicology screens during months 2 -12 were considered 'late failures.' Patients whose care was discontinued, or those who were lost to follow-up between months 2-12 of treatment were also included in this group. The reasons why patients were lost to follow-up were not accounted for in the study—if patients were not receiving toxicology screens at our institution, they were assumed to have relapsed. Finally, patients who were retained in care for 1 year with <4 positive toxicology screens during the latter 10 months of treatment were considered successes. We thus posit that minimal drug use (rather than complete abstinence) constitutes success. This approach draws upon former studies that used less stringent, more attainable definitions success; these definitions reflect a significant reduction in risk behavior instead of 'perfect performance,' and serve as more realistic target outcomes.[18,19]

TABLE 3: OUTCOMES GROUPS DEFINED

Outcome Group	Definition
Early Failure	• Treatment discontinued at discretion of physician, OR patient lost to follow up *< 8 weeks after induction*
Late Failure	• Treatment discontinued at discretion of physician, OR patient lost to follow-up *> 8 weeks, but <1 year after induction*, OR • Patients demonstrated ≥ 4 positive toxicology screens for opioids between 8 weeks and 1 year of treatment
Success	• Patient were retained in care for at least 1 year, with < 4 positive toxicology screens during the latter 10 months of treatment

IRB/Ethical considerations:

This project was approved by the Harvard Human Research Protection Program on 6/26/14, and by the MGH Internal Review Board on 7/22/14. Since this project did not involve any human interaction or intervention, the main ethical consideration was privacy and identity protection. Because information about drug use/treatment, psychiatric history, and criminal history is highly sensitive, every possible effort was made to maintain the privacy of the patients from whom data were collected. Medical records and sensitive information was only accessed using secure, password-protected, encrypted, and antivirus-enabled computers, and all sensitive information was accessible only to the primary researchers on the project. No breaches of data occurred.

Data Analysis

After collaborative efforts were made to determine the best approach to statistical analysis, all statistical programming and data output was performed by Joseph Locascio, with the support of Harvard Catalyst. The data analysis was performed in two general steps: First, preliminary chi-square tests and Fisher Exact tests were conducted to investigate the unadjusted relations of each categorical variable with the three outcome groups. T-Tests or nonparametric tests (Mann-Whitney, Kruskal-Wallis) were used for relations of categorical to continuous numeric variables, and correlations were used for continuous vs. continuous assessments. This exploratory exercise allowed us to filter out the most significant predictive variables for more fine-tuned, adjusted analysis.

Based on those initial results, in order to test *adjusted* multivariate relations between sets of categorical and continuous predictors to the study outcome, we performed a series of logistic regression analyses where the dependent variable in each case was a binary comparison formed by a pair-wise or pooled pair-wise contrast of the three addiction treatment outcome groups: Early Failure, Late Failure, and Success. In the separate analyses, the binary comparisons were: (1) pooled Early Failure and Late Failure vs. Success, (2) Early Failure vs. pooled Late Failure and Success, and (3) Late Failure vs. Success, (omitting Early Failure). Each analysis employed a backward elimination algorithm using a cutoff of $p=0.05$. The set of initial predictors for the comparisons involving the pooled categories were: age, sex, injection drug use, non-prescription

buprenorphine use, employment, hepatitis C seropositivity, non-prescription benzodiazepine use, years used, and participation in AA/NA. For the Late Failure vs. Success comparison, the predictors used were: percent early positive toxicology screens, drug counseling, injection drug use, hepatitis C positivity, cocaine use during treatment, employment, and participation in AA/NA.

III. Results

Demographics and Descriptive Statistics

A total of 160 patients were included in the final study. Of them, 104 (65%) were male and 56 (35%) were female. Ages ranged from 19-63 with an average of 33.3. Patients had actively used opioids for an average of 7 years before presentation. 152 (95%) were white. Full data on all collected patient characteristics can be found in Table 4, however a brief textual summary follows: 90 patients (56.3%) endorsed using injection drugs, and 67 (41.2%) endorsed using intranasally. Prior to induction, 52 (32.5%) endorsed actively using cocaine, 35 (21.9%) endorsed significant alcohol use, 122 (76.3%) were active cigarette smokers, 66 (41.3%) smoked marijuana, and 45 (28.1%) had used non-prescription benzodiazepines. 112 (73.7%) had used non-prescribed buprenorphine that they bought on the street. With respect to prior attempts at opioid abstinence, 104 (65.0%) had tried inpatient or intensive outpatient detoxification, 35 (21.9%) had tried methadone, and 38 (23.8%) had a prior attempt with buprenorphine. 48 (30.0%) endorsed a history of drug overdose. 82 (51.3%) were employed at the time of induction, 58 (36%) had been incarcerated in the past, and 35 (21.9%) had a history of homelessness. 78 (48.8%) carried a diagnosis of depression, 66 (41.3%) had an anxiety disorder, 28 (17.5%) had PTSD, and 14 (8.8%) had bipolar disorder. 49 (30.6%) suffered from chronic pain. 90 (56.3%) participated in in-house drug counseling, and 78 (48.8%) participated in AA/NA. 8 (5.0%) were HIV-positive, and 75 (46.9%) were seropositive for hepatitis C.

With respect to the outcome variables, 46 (28.8%) were classified as early treatment failures, 44 (27.5%) were classified as late treatment failures, and 70 (43.75%) were classified as treatment successes at the end of 1 year. Early failures averaged 30 years of age, late failures averaged 32 years of age, and successes averaged 36 years of age. 41 patients (25.73%) regularly used cocaine during the treatment period. With respect to

toxicology screens during the early treatment period, patients had an average of 4.6 screens each, and an average of 1.1 (23.9%) were positive for opiates.

Table 4: DEMOGRAPHIC AND DESCRIPTIVE DATA

Variable (Numeric)	**Mean Value (Years)**	**Range (Years)**
Age	33.3	19-63
Years of Active Drug Use	7	1-35
Variable (Categorical)	**Number Positive**	**Percent Positive**
Sex (M)	104	65.0%
Sex (F)	56	35.0%
Injection Drug use	90	56.3%
Intranasal Drug use	67	41.2%
Active Cocaine use	52	32.5%
Active Alcohol use	35	21.9%
Cigarette use	122	76.3%
Marijuana use	66	41.3%
Non-Rx Benzodiazepine use	45	28.1%
Non-Rx Buprenorphine use	118	73.7%
Prior Buprenorphine attempt	38	23.8%
Prior Methadone attempt	35	21.9%
Prior Detox attempt	104	65.0%
History of Overdose	48	30.0%
Employment status	82	51.3%
Prescribed SSRI	40	25.0%
Prescribed Benzodiazepine	17	10.6%
Prescribed Gaba-analogue	19	11.9%
Prescribed Antipsychotic	12	7.5%
Prescribed Mood Stabilizer	5	3.13%
Depression	78	48.8%
Anxiety Disorder	66	41.3%
Bipolar Disorder	14	8.8%
Psychosis	5	3.1%
PTSD	28	17.5%
Chronic Pain	49	30.6%
Race: White	152	95.0%
History of Incarceration	58	36.0%
History of Homelessness	35	21.9%
Drug Counseling	90	56.3%
Participation in AA/NA	78	48.8%
HIV Seropositivity	8	5.0%
Hepatitis C Seropositivity	75	46.9%

Table 5: OUTCOMES			
Outcome Group	**Number**	**Percent**	**Avg. Age (years)**
Early Failure	46	28.8%	30
Late Failure	44	27.5%	32
Success	70	43.75%	36

Unadjusted Predictive Relationships

Based on the number of 'positive' responses received, a total of 21 variables were investigated for unadjusted predictive relationships to outcomes. Of these, 5 variables achieved significance at the p<.05 level: Injection Drug Use, use of street buprenorphine, employment, attendance in drug counseling, and hepatitis C positivity. Accounting for multiple tests and using a more stringent p value of <.01, all variables but use of street buprenorphine remained significant. Importantly, these p values merely reflect the *distribution* of variables, and do not contain information about the *direction* of trends.

Table 6: UNADJUSTED RELATIONSHIPS OF PATIENT CHARACTERISTICS BY OUTCOME					
Variable	**N**	**Early Failure (%)**	**Late Failure (%)**	**Success (%)**	**P value**
OVERALL	160	46 (28.8)	44 (27.5)	70 (43.8)	
Sex (m)	104	35 (33.7)	29 (27.9)	40 (38.5)	.11
Sex (f)	56	11 (19.6)	15 (26.8)	30 (53.6)	
Injection Users	**90**	**32 (35.6)**	**30 (33.3)**	**28 (31.1)**	**.0012**
Non-Inj. Users	**70**	**14 (20.0)**	**14 (20.0)**	**42 (60.0)**	
Intranasal Users	67	20 (29.9)	18 (26.9)	29 (43.2)	.97
Non-In. Users	93	26 (27.9)	26 (27.9)	41 (44.2)	
Cocaine Users	52	17 (32.7)	17 (32.7)	18 (34.6)	.26
Non-Cocaine Users	108	29 (26.8)	27 (25.0)	52 (48.2)	
Alcohol Users	35	11 (31.4)	13 (37.1)	11 (31.4)	.20
Non-Alcohol Users	125	35 (28.0)	31 (24.8)	59 (47.2)	
Smokers	122	36 (29.5)	36 (29.5)	50 (41.0)	.42
Non-Smokers	38	10 (26.3)	8 (21.1)	20 (52.6)	

MJ Smokers	66	22 (33.3)	22 (33.3)	22 (33.3)	.082
Non- MJ Smokers	94	24 (25.3)	22 (23.4)	48 (51.1)	
Benzo Users	45	17 (37.8)	15 (33.3)	13 (28.9)	.058
Non-Benzo Users	115	29 (25.2)	29 (25.2)	57 (29.6)	
'Street' Bup Users	**118**	**31 (26.3)**	**39 (33.1)**	**48 (40.7)**	**.031**
Never Users	**42**	**15 (35.7)**	**5 (11.9)**	**22 (52.4)**	
Prior Bup Atmpt	38	11 (28.9)	12 (31.5)	15 (39.5)	.78
1st Bup Atmpt	122	35 (28.7)	32 (26.2)	55 (45.1)	
History of OD	48	16 (33.3)	16 (33.3)	16 (33.3)	.22
No History of OD	112	30 (26.7)	28 (25.0)	54 (48.2)	
Employed	**82**	**15 (18.3)**	**23 (29.1)**	**44 (53.7)**	**.006**
Unemployed	**78**	**31(39.7)**	**21 (26.9)**	**26 (33.3)**	
Depressed	78	19 (24.4)	24 (30.8)	35 (44.9)	.44
Not-Depressed	82	27 (32.9)	20 (24.4)	35 (42.7)	
Anxiety Disorder	66	16 (20.2)	18 (27.3)	32 (48.8)	.50
No Anx. Disorder	94	30 (31.9)	26 (27.7)	38 (40.4)	
PTSD	28	6 (21.43)	11 (39.3)	11 (39.3)	.29
No PTSD	132	40 (30.3)	33 (25.0)	59 (44.7)	
Chronic Pain	49	8 (16.3)	17 (34.7)	24 (50.0)	.0620
No Chronic Pain	111	38 (34.2)	27 (24.3)	46 (41.4)	
Past Incarceration	58	20 (34.5)	18 (31.0)	20 (34.5)	.19
No Past Incarc.	102	26 (25.5)	26 (25.5)	50 (49.0)	
Once Homeless	35	10 (28.6)	9 (25.7)	16 (45.7)	.95
Never Homeless	125	36 (28.8)	35 (28.0)	54 (43.2)	
Drug Counseling	**90**	**16 (17.8)**	**21 (23.3)**	**53 (58.9)**	**<.0001**
No Drug Counsel.	**70**	**30 (42.9)**	**23 (32.9)**	**17 (24.3)**	
AA/NA Attenders	78	16 (20.5)	24 (30.8)	38 (48.7)	.08
No AA/NA	82	30 (36.6)	20 (24.4)	32 (39.0)	
Hep C Positive	**75**	**27 (36.0)**	**25 (33.3)**	**23 (30.7)**	**.0073**
Not Hep C. Pos	**85**	**19 (22.4)**	**19 (22.4)**	**47 (55.2)**	

Logistic Regression for Adjusted Predictors

Three logistic regression models were run. They are presented below in order, accompanied by charts summarizing the backward elimination process, and graphic depictions of their respective predictive models.

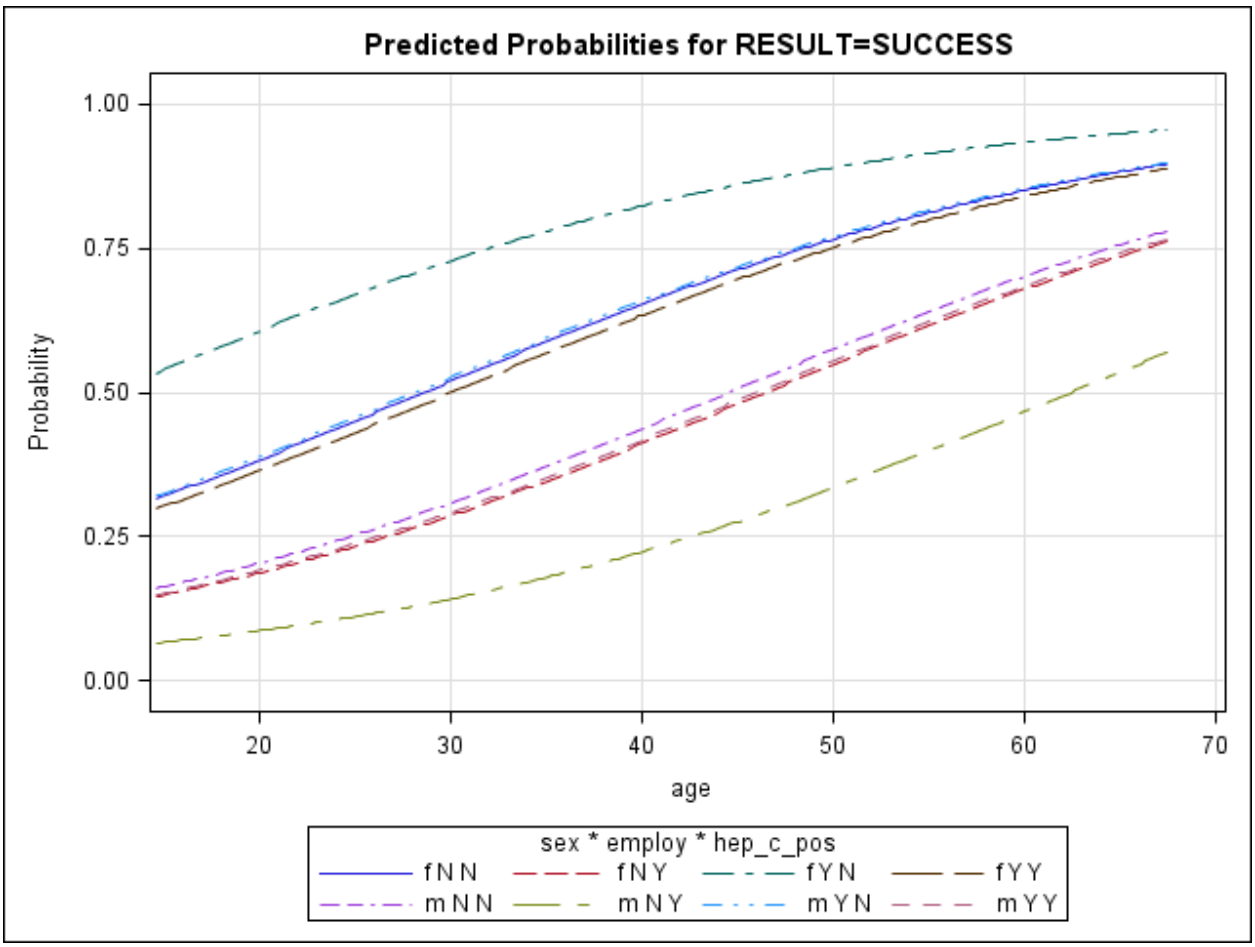
1. Success vs. Early or Late Failure

For the logistic regression whose outcome comparison was pooled early failures and late failures vs. success, the final reduced model included the predictors Age (p= .0013), Sex (p= .0200), Employment (p= .0131), and Hepatitis C seropositivity (p = .0062). Age, employment, and female sex were all correlated positively with success. Having hepatitis C was correlated with failure. Odds ratio estimates with confidence intervals (CIs) follow: For every additional decade of age, individuals were 1.7x more likely to respond successfully to treatment (CI 1.25-2.47). Women were 2.42x more likely than men to be successful (CI 1.16-5.18). Those who were employed at the time of induction were 2.48x more likely to be successful (CI 1.22-5.1). Finally, those who were seropositive for hepatitis C were 2.70x more likely to be in the early or late failure group (CI 1.33-5.56). The area under the ROC curve for this model was .736.

Table 7: SUMMARY OF BACKWARD ELIMINATION: SUCCESS vs. FAILURE AT ANY TIME

Elimination	Variable	P value	Predicts	Odds Ratio	Confidence Interval
1	Years Used	0.8635		Eliminated	
2	Streep Bup	0.3855		Eliminated	
3	AA/NA	0.2573		Eliminated	
4	Non-Rx Benzo	0.2920		Eliminated	
5	Inj. Drug Use	0.1524		Eliminated	
Sustained	Age (Decades)	*0.0013*	Success	1.74	1.25-2.47
Sustained	Sex (Female)	*0.0200*	Success	2.42	1.16-5.18
Sustained	Employment	*0.0131*	Success	2.48	1.22-5.1
Sustained	Hepatitis C	*0.0062*	Failure	2.70	1.33-5.56

Figure 1: PREDICTIVE MODEL FOR SUCCESS (vs. FAILURE AT ANY TIME) **See appendix for legend

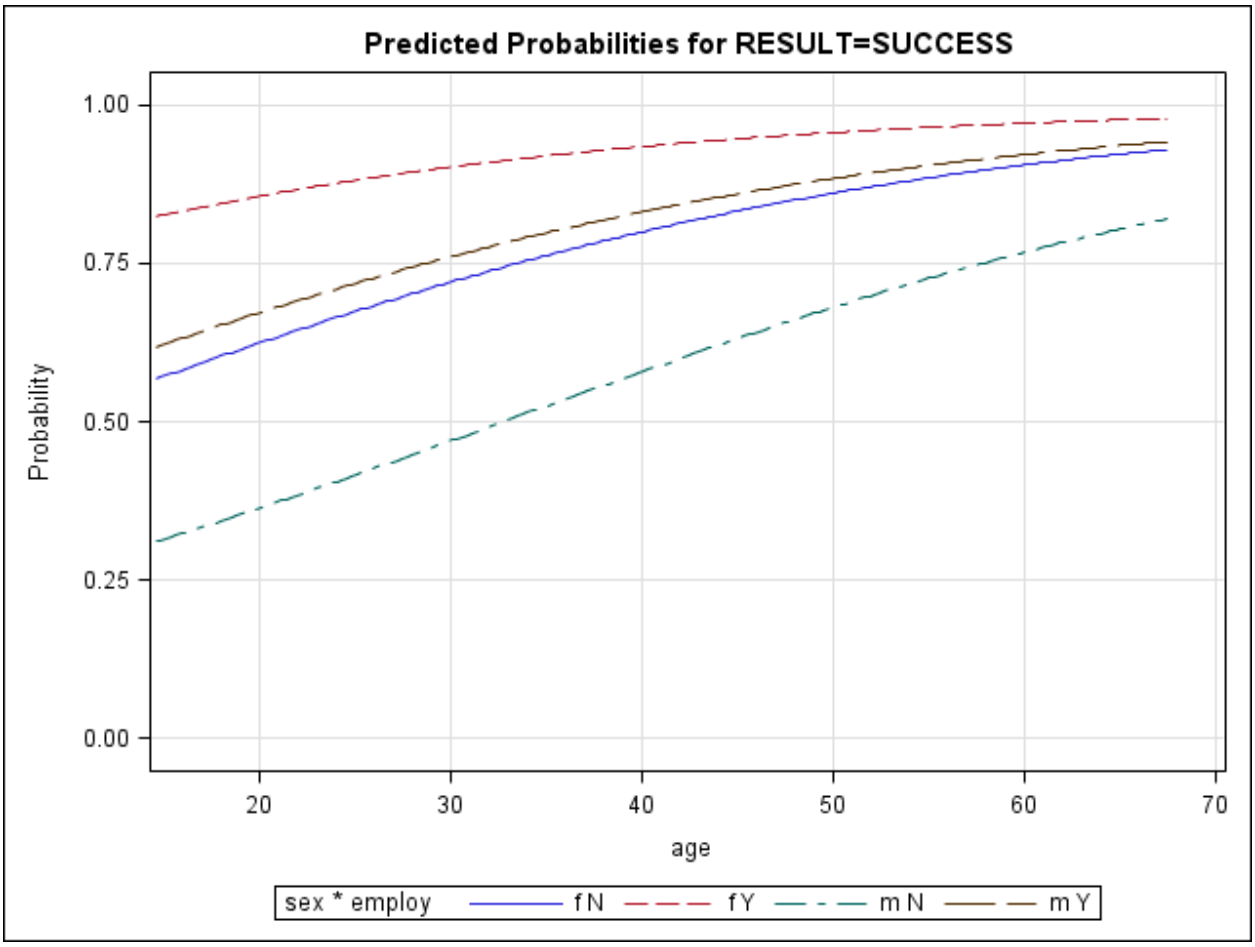


2. Early Failure vs. Pooled Late Failure/Success (Treatment Retention)

For the logistic regression whose outcome comparison was early failure versus pooled late failures and success, the final reduced model included the predictors: Age (p= .0197), Sex (p= .0123), and Employment (p=0.0011). Increased age, female sex, and employment were all correlated with treatment retention greater than 2 months. Conversely, young age, male sex, and unemployment were specifically associated with early failure. For every additional decade of age, patients were 1.55x more likely to successfully exhibit treatment retention past the early phase (CI 1.09-2.29). Females were 2.99x as likely to achieve treatment retention (CI 1.29-6.99), and those who were employed were 3.59x as likely to achieve treatment retention (CI 1.70-7.92). The area under the ROC curve for this model was .715.

Table 8: SUMMMARY OF BACKWARD ELIMINATION: TREATMENT RETENTION > 8 WEEKS					
Elimination	**Variable**	**P value**	**Predicts**	**Odds Ratio**	**Confidence Interval**
1	Years Used	0.9958		Eliminated	
2	Non Rx Benzo	0.4843		Eliminated	
3	Inj. Drug Use	0.4484		Eliminated	
4	Street Bup	0.1736		Eliminated	
5	Hep C Pos	0.1387		Eliminated	
6	AA/NA	0.1820		Eliminated	
Sustained	Age (decades)	*0.0197*	Retention	1.55	1.09-2.29
Sustained	Sex (F)	*0.0123*	Retention	2.99	1.29-6.99
Sustained	Employment	*0.0011*	Retention	3.59	1.70-7.92

Figure 2: PREDICTIVE MODEL FOR TREATMENT RETENTION > 8 WEEKS **See appendix for legend



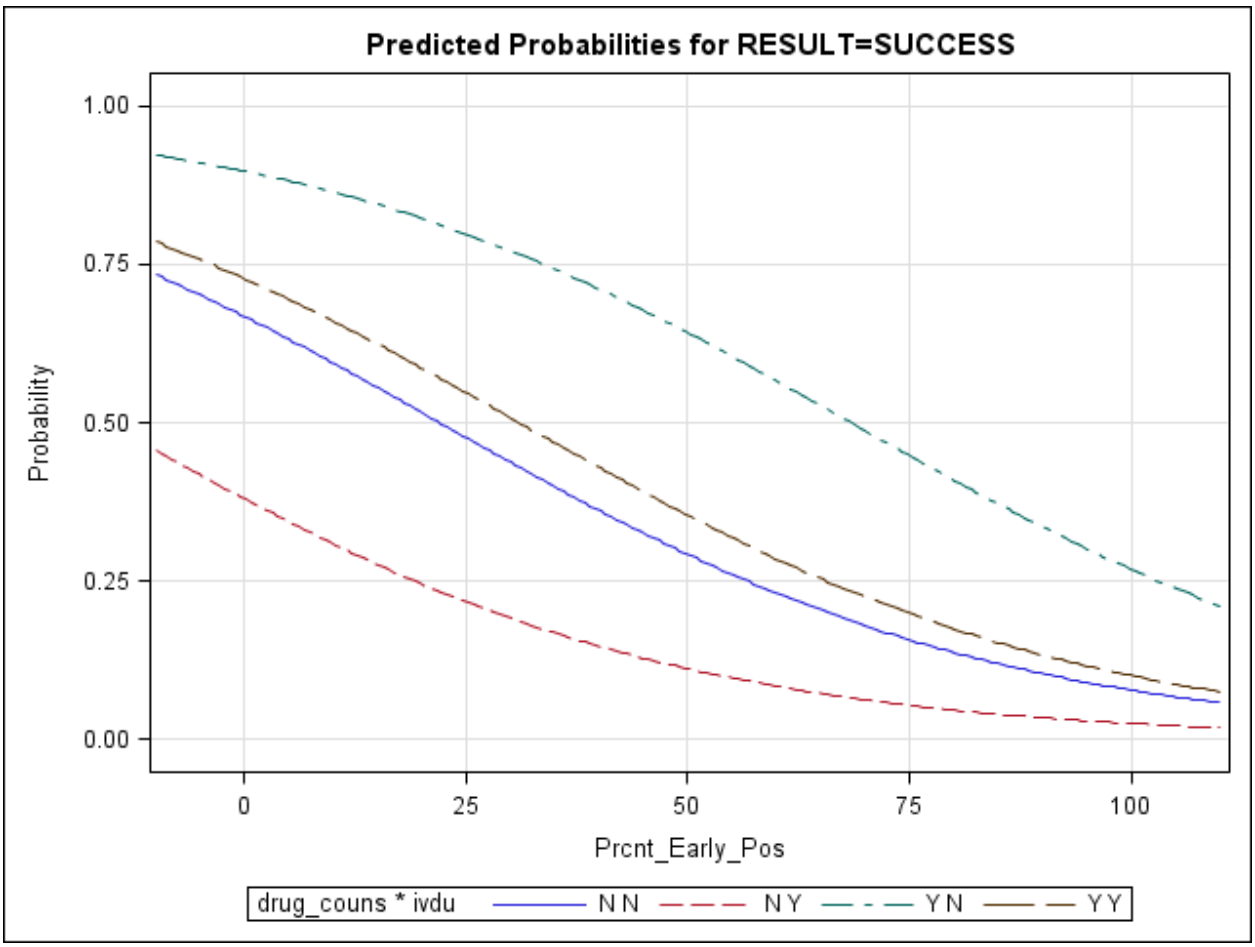
3. Late Failures vs. Success (excluding Early Failures)

Finally, for the logistic regression whose outcome comparison was Late Failures vs. Successes (excluding early failures), the final reduced model included the predictors: Early Percent Positive Toxicology Screens (p=.001), Participation in Drug Counseling (p=.002), and Injection Drug Use (p=.010). Increased percentage early positive drug screens and history of Injection Drug Use were both significantly predictive of late failure. Participation in Drug Counseling was significantly predictive of success. For every additional 25% of early toxicology screens that were positive, patients were predicted to be 2.2x more likely to fall into the late failure, rather than the success group (CI 1.42-3.70). Participation in Drug Counseling made it 4.3x more likely that patients would fall into the success group, rather than the late failure group (CI 1.76-11.58). Finally, patients who had a history of Injection Drug Use were 3.28x more likely to be late failures, rather than successes (1.35-8.40). The area of the ROC curve for this predictive model is .801.

TABLE 9: SUMMARY OF BACKWARD ELIMINATION: LATE FAILURE vs. SUCCESS

Elimination	Variable	P value	Predicts	Odds Ratio	Confidence Interval
1	Tx Cocaine	0.9836		Eliminated	
2	AA/NA	0.5949		Eliminated	
3	Employment	0.5532		Eliminated	
4	Hepatitis C	0.2152		Eliminated	
Sustained	Early % Pos (25%)	*0.0010*	Failure	2.21	1.42-3.70
Sustained	Drug Counseling	*0.0020*	Success	4.36	1.76-11.58
Sustained	Inj. Drug Use	*0.0104*	Failure	3.28	1.35-8.40

Figure 3: PREDICTIVE MODEL FOR SUCCESS vs. LATE FAILURE **See appendix for legend



IV. Discussion

Demographic/Unadjusted Results in Context

First, with respect to demographics, our population very closely mirrors that described by the 2014 JAMA study documenting the changing face of opioid addiction. Both reflect a population of >90% white individuals in their late 20's/early 30's, living in urban/suburban regions.[15] Interestingly, the fact that nearly 50% of our patients had never tried injection drugs reflects the concurrent evolution of opioid addiction towards prescription medications.[20] As expected, our population also exhibits higher rates of other recreational drug use, mental illness, history of incarceration, and markers of lower socio-economic status (unemployment, history of homelessness) than the general population.

Of particular interest are the rates of drug-associated infectious diseases in this population: while only 8 patients (5% of our population) were HIV positive, 75 (46.9%)

were hepatitis C positive. This reflects a concerning national trend. There has been a significant increase in the prevalence of hepatitis C in young, suburban, injection drug users, and disease and death resulting from hepatitis C infection in the United States has recently surpassed that caused by HIV.[21] In our study, 90 patients had used injection drugs, and of them 64 (71%) were hepatitis C positive. Only 11 patients who were hepatitis C positive denied injection drug use, which may represent underreporting plus hepatitis C from other causes, such as intranasal use or sexual contact. Rates of hepatitis C at this high level are uncommon, but have been reported elsewhere in the literature.[22]

The overall rates of successful response to buprenorphine (in our study: 43.75%) are comparable to prior studies done in this area. For example, our rates are slightly lower than the smaller 2007 study examining an overlapping population, which found a 54% success rate at 6 months.[11] Of course, success rates depend intrinsically on how studies define 'success,' in that studies using longer follow-up periods are likely to define fewer individuals as successful. Further, because individuals who left treatment were counted as 'failures' regardless of their reasons for leaving, it is possible that some patients in our early or late failure groups actually maintained sobriety on their own, or under the care of non-MGH CHCC physicians. Importantly, in our study, rates of success varied dramatically across specific demographic groups. For example, the average male had a 38.5% chance of success, whereas the average female had a 53.6% chance of success. Patients with a history of injection drug use had a 31.1% chance of success, and those who were unemployed had a 33.3% chance of success. Those with hepatitis C had a 30.7% chance, and those who did not attend early drug counseling meetings had only a 24.3% chance of success.

With respect to the probability of early failure specifically, compared with a baseline overall average rate of 28.8%, people who used recreational benzodiazepines had a 37.8% chance of failing treatment in the first 8 weeks. Those who did not attend drug counseling had a 43.9% chance of falling into this group. On the other hand, those who were employed at the time of induction only had an 18.3% chance of early failure. Patients with chronic pain had only a 16.3% chance of failing early, and those who attended AA/NA had only a 20.5% chance. Interestingly, those who were most likely to fall into the 'late failure' group were regular Alcohol Users (37.1%) and those with PTSD (39.3%).

It is important to interpret all of these data with care. While these unadjusted results are *predictive* (especially those which reached significance), it is impossible to tell which variables are *operative* with respect to the outcome. In order to parse the independent contributions of each variable to the outcome group, and to see how the probability of a particular outcome is effected by *overlapping* characteristics, it is necessary to invoke logistic models.

Adjusted Logistic Regressions: Interpretation

1. Predictors of Success over Failure at any Time

This grouping reflects the traditional success/failure dichotomy used by nearly all prior studies, and answers the question: What are the predictors that a patient will be successful at the end of one year of therapy? Our study suggests that older employed females with no history of hepatitis C have the greatest chance of successful response to buprenorphine. Conversely, younger, unemployed males with hepatitis C have the smallest chance of success. According to the predictive model, a 20-year-old unemployed male with hepatitis C has an estimated <10% chance of successful response to treatment. On the other hand, an employed 50 year old woman with no hepatitis C history has >80% chance of succeeding.

Age and employment are both documented predictors of successful response to medical treatment of opioid addiction. [11,13,14] However, far fewer studies have uncovered an independent connection between Hepatitis C and response to opioid replacement therapy. In one example, a study published in early 2015 investigated data from the National Drug Abuse Treatment Clinical Trial Network, and found that patients with HCV seropositivity were less likely to submit opioid negative urines during or after treatment with buprenorphine.[23] It is notable that injection drug use was eliminated from this backward prediction model with a p value of .1524. What is it about hepatitis C itself that portends failure? Our interpretation is that the relationship is not a consequence the disease, but rather a function of the risks associated with hepatitis C exposure. In most circumstances, hepatitis C among injection drug users results from unsafe needle practices, such as sharing needles/cottons/cookers. It is possible that individuals who have resorted to using unsafe needle practices share certain personal or psychosocial characteristics, which also make it

harder to overcome addiction. Possible candidates for such a characteristic include desperation to use despite inappropriate equipment (a possible reflection of the strong grip of addiction), a reckless/risk avid personality type, or socioeconomic inability to procure clean supplies.

2. Early Failure vs. Treatment Retention > 8 weeks

This analysis dichotomized all individuals who failed during the first 8 weeks of treatment (Early Failures), against those who were successfully retained past two months of treatment, regardless of the ultimate outcome. It was designed to answer the question: How can we predict which people are at the highest risk of *early* failure? Or, how can we predict who has a better chance of treatment retention? Our study suggests that a simple model of age, sex, and employment is sufficient to predict probability of early failure. Those who are young, male, and unemployed are at the highest risk in the early period, such that a 20 year old, unemployed male has a >65% chance of failing treatment during the first eight weeks. This result supports and validates the results of the prior regression, in which young unemployed males were found to be in the highest risk group. However, in this test, injection drug use rather than hepatitis C status was found to have predictive relevance.

Why is injection drug use a predictor for early failure? The above hypotheses invoked to explain the role of hepatitis C may be relevant. However, there are additional factors that may also be at play, for example, the rapidity by which an injected drug reaches the brain, producing the characteristic quick intense feeling of euphoria, followed (especially in the case of injected heroin) by the rapid metabolism of the drug and the onset of withdrawal. These differing pharmacodynamic properties of injection drugs likely contribute to a documented increase in their addictive potential.[24] Additionally, the *act* of injecting drugs may be elevated to a ritualistic behavior by some individuals—one that is an integral part of the totality of addiction. While patients who use oral opioids may find a more natural, analogous opioid replacement in a pill of buprenorphine, patients who are accustomed to injecting might not get the same satisfaction. An analogy can be drawn between this phenomena and that of why some cigarette smokers may have trouble quitting simply by using a nicotine patch; merely replacing the biochemical drug medically may not be sufficient, insofar as addiction extends beyond pure biochemical dependence

into a more complex, biopsychosocial realm. Importantly, our study does not suggest that injection drug users would be better off taking other forms of opioid replacement therapy—instead, it only suggests that independent of other factors, those patients have the highest risk of early failure when taking buprenorphine.

3. Late Failures vs. Successes

This model, which excluded the early failures, was designed to find early predictors that might be able to portend failure later in treatment, among those patients who were successfully retained past the first eight weeks. Indeed, approximately 50% of patients who failed treatment did so in the latter 10 months of care, indicating that patients are still at significant risk after they surpass the early stage of treatment. Our findings suggest that three variables function as successful predictors of this later failure: Percentage positive early toxicology screens, participation in drug counseling, and injection drug use.

First, the higher the percentage of toxicology screens during the first 8 weeks of treatment that were positive, the more likely patents were to fall in the late failure group. This result suggests that patients who exhibited difficulty in attaining abstinence early on are at higher risk for relapse or failure later on. These results indicate that those factors which cause a given patient to have a slow or difficult time adjusting to sobriety/buprenorphine therapy probably remain present and relevant during the entire treatment period. At least one other study has corroborated this result, showing that response after as little as two weeks of therapy is sufficient to predict performance after 12 weeks of treatment.[25]

Finally, participation in drug counseling is a strong positive predictive factor for long-term success. This shows that patients who attended 3 or more sessions in the first 1-2 months of treatment were 4.5x more likely to succeed. The role of drug counseling is thus far unsettled in the literature. One retrospective secondary analysis found a modest benefit of counseling specifically among injection drug users, but only those who were also adherent to treatment.[26] However, a 2011 multisite randomized controlled trial found no difference between the outcomes in counseling vs. no-counseling groups.[19] Another recent randomized trial investigated the role of a specific, new therapeutic approach and failed to find significant differences between groups who were or were not exposed to therapy.[27]

One issue with this particular research question is that there is no standardized protocol for clinic or hospital based therapy sessions—'therapy' or 'counseling' can mean widely divergent things. Even within this study, the content of counseling appointments was diverse, including both individual and group sessions, with varying emphasis on mental illness and psychopharmacology versus simply social or economic issues. In any case, it is clear that in our cohort, at the very least, willingness to participate in therapy sessions is a positive prognostic indicator. At the most, participation in therapy provided patients with support and/or tools that they could use to avoid the mental or physical states and environments that put them at risk of using drugs again.

Learning from Non-Predictive Variables

In addition to investigating the predictive variables, it is important to also take stock of all of the variables that were *not* predictive—those which had no statistical relationship with outcomes. Of special note, the use of any other drugs (alcohol, cocaine, cigarettes, marijuana, benzodiazepines) either prior to or during the study (in the case of cocaine) predicted success or failure. While the practice in the clinic was to discourage all other drug use (especially the use of substances which might lower the inhibitions of the user, such as alcohol or benzodiazepines), this result suggests that patients were just as likely to achieve success regardless of whether they had used non-opioid drugs. Also, it was not common practice to discontinue care based solely on positive toxicology screens for cocaine or marijuana; these results help to validate that practice as a reasonable harm reduction technique. Next, while mental health comorbidities were highly overrepresented in our population, neither psychiatric diagnoses nor the medications used to treat them provided predictive value in this model. It is important to mention that mental health problems can be difficult to parse from addiction itself—many DSM criteria purposefully exclude diagnoses that could be attributed to substance use rather than organic causes. Despite this, our results cast an optimistic light on the prospects of individuals who suffer from concurrent mental illness and addiction.

'Years of active drug use' was also non-predictive, perhaps counter-intuitively. One might hypothesize that if a person had been using for more time, their psychosocial habits and/or their brain chemistry would be more firmly set, thus creating a 'steeper climb' out

of the grip of addiction. However, the youngest patients, many of whom had only 1-2 years of drug use actually fared the worst. The reasons for this are elusive—perhaps older patients (who averaged more years of drug use) have developed more personal maturity and motivation to stop using drugs. Another possible hypothesis is reflected in the language of 'hitting rock bottom' that is used in addiction circles, describing the period at which a person experiences enough loss that they are 'fed up' with using in a deep and profound sense. Perhaps younger patients who are new to opioid addiction have yet to experience this state, or fully appreciate the long-term toll of addiction.

Finally, the use of street buprenorphine has been uncovered as a positive prognostic indicator in a large recent study.[14] Our unadjusted results did show that individuals who had used street buprenorphine were unevenly distributed among the outcome groups. However, this characteristic failed to reach significance in the logistic models. It is possible that patients who have tried buprenorphine already are personally aware of the medication's value. While some might find that they feel 'high' when taking buprenorphine, evidence suggests that illicit use rarely results in euphoria, and instead serves to stave off the noxious symptoms of withdrawal, pain, or depression.[28] Unfortunately, this study sheds little light on the meaning of illicit buprenorphine use, and interesting questions remain about the actual impact of buprenorphine diversion on public health.

Limitations

The most important limitation of this study is that it is retrospective and involves no control population or active intervention. Treatment protocols were not enforced, and variables could only be controlled mathematically. For that reason, it can be used only to determine correlations between variables. Importantly, while these correlations may theoretically have predictive value with respect to future patients, the model has not yet been validated in any other population, so results should be applied with caution. Also, the relationships between patient characteristics and outcomes cannot be considered causal, and for this reason, actively manipulating any specific characteristic of a particular patient (say, participation in drug counseling) may have no effect on that patient's outcome, even if that characteristic was predictive in our model. Finally, the study is limited to one primary

care practice, and care must be taken when trying to generalize these results to other practice types in other areas of the country.

Conclusions

The population we studied reflects the changing demographics of opioid addiction, and exhibits high rates of concurrent non-opioid drug use, mental illness, incarceration, homelessness, and hepatitis C. Our overall buprenorphine one-year success rate of 43.8% was on par with other studies in similar settings. However, we found that a given patient's individual chances of success can vary greatly depending on certain characteristics. These trends are evident when single variables are investigated in isolation—for example, injection drug users, patients who are unemployed, are Hepatitis C positive, and who do not participate in drug counseling are less likely to succeed. However, the trends were amplified when we investigated overlapping traits in logistic regression models. The traits that are most associated with success at one year are female sex, increased age, employment, and hepatitis C *negativity.* Combinations of these four variables predict a wide ranging probability of success, from as low as 10% chance of success for a 20 year old unemployed male with hepatitis C, to an 80% chance for a 50 year old employed woman with no history of hepatitis C exposure.

In secondary analyses, we also found that employment, female sex, and negative history of injection drug use all predict treatment retention past 2 months, such that a 50 year old woman with no history of injection drug use is 3x more likely than a 20 year old male IV drug user to be retained in care. We also found that the percentage of early positive toxicology screens, and early failure to participate in counseling both predict treatment failure later in the course. Finally, we found that the use of non-opioid drugs before treatment, use of cocaine during treatment, the presence of mental illness, history of overdose or incarceration, and prior treatment exposures all have no predictive power with respect to ultimate outcomes.

While the study serves best to generate hypotheses for future studies, our results suggest a few clinical lessons. First, it appears centrally important to understand the individual risk profiles of patients who are candidates for buprenorphine therapy. Given our data, it seems very likely that different patients require different levels of observation

and support in order to achieve the same chances of success. Physicians should be aware of each patient's positive or negative prognostic indicators, and adjust their care accordingly. These risk factors include a 'bumpy' start on buprenorphine, defined by numerous positive toxicology screens early in treatment, and failure to participate in supplemental addiction therapy. Lastly, we caution physicians who are tempted to discontinue therapy with buprenorphine based on patient use of non-opioid drugs—cocaine in particular. Buprenorphine is a medication specifically designed to treat opioid addiction, and should not be expected to aid poly-substance users in abstaining from non-opioid drugs. Our data suggests that patients have the same ultimate chances of successfully attaining sobriety from opioids, whether or not they use non-opioid drugs. Therefore, our data supports continuing cocaine-using patients on buprenorphine while providing them with additional support to treat their other addictions.

Suggestions for future work

Much is yet to be learned about how best to use buprenorphine to tread addiction. One logical next step would be to validate the results of this study, and determine whether our models are actually predictive in other populations. The best way to do this would be using a prospective cohort study, in which patients are asked about the characteristics of interest *before* initiating therapy, and data are collected about how patents fare. The predictive algorithms generated here would be applied to this population, and tested for predictive strength. If our models were to evolve and become validated in multiple, larger populations, it would be possible to generate a simple tool that physicians could use to risk stratify their patients as they enter treatment. The tool could take the form of a 'score,' which could be easily translated into an individualized probability of success or failure. Based on a patient's score, a physician could alter the frequency of follow-up or counseling visits, the dose/scheduling of buprenorphine, or spend more time focusing on cultivating a strong therapeutic relationship. In conclusion, we hope that these results will help support an approach to addiction care that is both more evidence-based, and more personal at the same time.

V. Acknowledgments

I would like to acknowledge Mark Eisenberg for his generous support and guidance from this project's genesis to its completion, for introducing me to such an important and far-reaching topic, and for exemplifying the level of compassion and understanding that is too often denied to patients who struggle with addiction. I would also like to thank Jim Morrill, Sarah Wakeman, and James Meigs for their helpful suggestions about project design, James Meigs for introducing me to RedCap, and Jim Morrill for introducing me to RPDR. Finally, I greatly appreciate the contribution of Joe Loscasio, who worked with me to design a statistical approach to this project, executed the primary statistical analyses, and aided me in their interpretation. This work was conducted with support from Harvard Catalyst, made possible by the Harvard Clinical and Translational Science Center (NCRR and NCATS, NIH Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers.

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VII. Appendix

Figure 1 Legend

X axis: Age; *Y axis:* Probability of falling into the 'Success' group

Interpretation: The 3-letter sequences (ie. fNN, etc.) in the small box below the graph represent all possible combinations of the characteristics sex, employment status, and hepatitis C seropositivity respectively, such that f = Female, m = Male, Y = Yes, and N = No. Thus, 'FNN' can be interpreted as 'Female' 'Not employed' and 'Not hepatitis C positive.' 'mYY' can be interpreted as 'Male,' 'Employed,' and 'Hepatitis C positive.' Each combination of personal characteristics corresponds with a line on the graph as dictated by a unique color and pattern combination. Each line on the graph quantifies the predicted probability that a person will fall into the 'success group,' given their age and any given combination of predictive characteristics.

Figure 2 Legend

X axis: Age; *Y axis:* Probability of falling into the 'Success' group

Interpretation: This graph can be read using the same general approach as in Figure 1. In this case, all 2-letter sequences in the small box below the graph represent possible combinations of sex and employment, respectively, such that f = Female, m = Male, Y = Yes, and N = No. Thus, fN means 'Female, Unemployed,' 'fY' means 'Female, Employed,' etc. As with Figure 1, each 2-letter combination corresponds with a line on the graph, which represents the predicted probability that a person will fall into the 'success group,' given their age and a given combination of predictive characteristics.

Figure 3 Legend

X axis: % Positive Toxicology Screens in the first 8 weeks of Treatment; *Y axis:* Probability of falling into the 'Success' group

Interpretation: This graph can be read using the same general approach as in Figures 1 and 2. All 2-letter sequences in the small box below the graph represent possible combinations of drug counseling participation and injection drug use, in that order, such that NN means 'No counseling, No injection drug use,' and NY means 'No counseling, Yes injection drug use,' etc. As with Figures 1 and 2, each 2-letter combination corresponds with a line on the graph, which represents the predicted probability that a person with that combination of characteristics at a given age will fall into the 'success' group.